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Division of Lung Diseases

National Heart and Lung Institute

Workshop Report

Prostaglandins and the Lung

January 21 and 22, 1976

Airlie, Virginia

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

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On January 21 and 22, 1976, thirty-one investigators met at Airlie House, Warrenton, Virginia, to participate in a workshop on "Prostaglandins and the Lung," sponsored by the Division of Lung Diseases of the National Heart and Lung Institute. Wide-ranging interests in biochemistry, pharmacology, physiology, and clinical medicine were represented. The following is a summary of the talks and discussions, the unanswered questions, and the recommendations. The report is presented to the "pulmonary research community" in order to make the results of these discussions more widely available. It is organized along the lines of the agenda. The report was prepared by Dr. Sami Said and Dr. Peter Ramwell, co-chairmen of the workshop.

Biochemistry of Prostaglandins and Related Substances

The significance of many of the early metabolic studies of the prostaglandins in 1974 and 1975 by the Dutch, Swedish and Japanese groups is now apparent. It is clear that the prostaglandins are part of a multi-branching cascade derived from the polyenoic precursor fatty acids and that the individual components of the cascade have different biological properties. Moreover, different tissues yield different proportions of these components. The rate-limiting step in the initiation of this cascade appears to be the release of the appropriate polyenoic fatty acid precursor such as arachidonic acid (AA).

There is urgent need to know the relative contribution of cholesterol esters, phospholipid and triglyceride as sources of arachidonate. Little is known of the nature of the acyl hydrolases involved and what is the mechanism of activation. Even less is known of the mechanisms involved in the release of the other precursors, dihomo-gamma linolenic and eicosapentenoic acids. The properties of the individual components of the cascade derived from these latter two precursors must be different from the properties of the components already identified in the arachidonic acid cascade. This is to be expected because PGE_1 is known to have markedly different effect on platelets in contrast to those of PGE_2; similarly, dihomogamma linolenic acid inhibits platelet aggregation *in vitro* and *in vivo* in contrast to arachidonic acid which yields aggregating substances.

Of particular interest is one of these aggregating substances, thromboxane A2, which has recently been identified and whose structure has been published - but not independently confirmed. This compound, which is derived from prostaglandin endoperoxide G2, may have a role in normal platelet function but since many of the initial studies have been carried out in washed platelets, the precise physiological and pathological significance of the formation of this compound in platelets remains to be determined.

Similarly, thromboxane A2 appears to be a constitutent of "rabbit aorta contracting substances" and therefore its effect on smooth muscle, especially pulmonary and coronary muscle, is of interest too. Clearly, good and swift analytical methods are needed for these compounds. Fortunately, the stable product of the short lived thromboxane A2 (40 sec) namely thromboxane B2, appears when coupled to protein, to be powerfully antigenic; antibodies have been easily raised. There is a clear and urgent need to make available these materials as well as the endoperoxides (which are stable in organic solvents), and the appropriate antibodies.

The biological studies of the endoperoxides and thromboxane A2 are limited and it is necessary to move from the isolated tissue and organ preparation to in vivo studies on primates as soon as possible. The complicated species differences that have been observed in response to prostanoate and nonprostanoate compounds make such a progression important. This is especially true in view of the marked species differences also observed in the nature of the different cascades derived from the various polyenoic precursor acids.

Much needs to be done to "profile" the arachidonic acid cascade in different physiological and pathological situations. At present this is being done only in washed platelets and during the reproductive cycle. Such a profiling procedure requires provision of authentic intermediates, their pharmacological antagonists and specific enzyme inhibitors. In this manner it is hoped to obtain a clearer idea of the consequences of the release of the polyenoic precursor acids and the pathological relationships of the initiating steps. Work to this end is being accomplished by studying the effect of arachidonic and dihomogamma linolenic acid on pulmonary, systemic, femoral, renal and mesenteric blood flow in dogs in the presence and absence of aspirin and indomethacin. Powerful vasoconstrictor effects are observed in the isolated pulmonary lobe preparation and these remarkable effects can be mimicked by synthetic endoperoxide analogs. In the kidney, increased blood flow and renin release occurs with the polyenoic precursors.

The cardiovascular effects of the precursor acids is independent of the presence of platelets. In consequence, the precise site of the metabolism of the precursors needs to be determined. At present cytochemical techniques are not adequate and effort in this direction is required. In this context, knowledge is needed of the cellular localization of the acyl hydrolases responsible for providing the precursor acids as a result of septicemia, trauma, ischemia, hemorrhagic shock, etc.

The basic features of prostaglandin catabolism to C_{16} structures have now been delineated. Unfortunately, quantitative knowledge of the biological properties of the metabolites in vivo is still sparse. Moreover, the conditions of the tissues and how they effect metabolism is unknown. For example, the effects of pulmonary edema or of hypoxia on arachidonic acid metabolism have not been studied in detail.

Some progress has been made in measuring pulmonary metabolism in vivo in humans but this work is limited and difficult. The data obtained tends to be restricted to single patients in most instances. The results show that human lung metabolizes on a single transit, most of the PGE, but not the PGA compounds.

Obviously more human studies involving cardiac catheterization, hemodialysis, extracorporeal surgery, hypothermia and other procedures are desirable. The extensive use of Swan-Ganz catheters should provide good conditions for sampling and pressure measurement. Studies of metabolism in shock and trauma are necessary. Knowledge of the sites of transport and metabolism of prostanoate and nonprostanoate compounds in the human lung is virtually nonexistent.

The effects of aspirin and other drugs commonly used in the arthritis clinic on the cytochemistry of the enzymes of the arachidonic acid cascade must be determined. Surprisingly, little is known of the role of the metabolic systems in sensitized human tissue. Nothing is known of the disruptive effects of endotoxin or hypoxia on the subcellular elements with which the

enzyme systems are associated. Finally, nothing is known of the cell physiology of prostaglandins in isolated myocardial or pulmonary cells. At the membrane level, little is known, for example, of the relation of prostaglandin binding and adenylate cyclase stimulation in these tissues. Part of the problem lies with the increasing complexity of the prostaglandin systems, their ubiquity and their powerful effects on nearly every cell type studied. This means that investigators require a high degree of sophistication in their background knowledge and efficient updating of procedures with the rapid progress of the field. Attention could be paid to the possibility of a systematic series of mini courses.

Of considerable importance is the complex and bewildering relationship of the arachidonic acid system to the biogenic amines, kinins, and steroids. Numerous examples now exist of the close relationship of the responses of catecholamines to the prostaglandins in modulating tone in pulmonary and other types of smooth muscle. Another complexity lies in the relationship of such compounds and the kinins in releasing prostaglandins. For example, bradykinin owes its action in part to release of prostaglandins. The relationship of drugs to the prostaglandin system is also being scrutinized owing to the widespread use of prostaglandin synthetase inhibitors. For example, aspirin or indomethacin can render diuretics such as furosamide quite ineffective.

The three procedures available are radioimmunoassay (RIA), gas chromatography mass spectrometry and bioassay. Scintillation counters and transducer-recorder equipment are not inexpensive items especially when one adds the special pipettes, mixing equipment, glassware, pumps and computer programs. Nevertheless, the capital cost of the mass spectrometer is much higher and the particular problem is that the equipment needs to be dedicated to prostaglandin analysis. The problem is not the separation steps since high pressure liquid chromatography is now available. The real problem is the sensitivity of the detector system which needs to sense a mass of at least 10-100 picograms. However, the large number of closely related prostanoate and nonprostanoate compounds makes identification based on one chromatographic system, a not entirely certain proposition.

The three systems are quite complementary in that the bioassay can give an immediate readout during the experiment. RIA permits the processing of a large number of samples in parallel. Mass spectrometry permits definitive analysis but the equipment performs analysis in series with a corresponding greater time requirement.

Several steps can be taken to improve matters. The preparation of more specific antibodies - especially to the PGE series and to thromboxane B2 - is needed. Better radioisotopes are required; ^{14}C labelling of the ring carbons (C_8 - C_{12}) and ^{14}C labelling in different positions of the carbons of the precursor polyenoic acids would be most useful.

In the mass spectrometry field there is a major requirement to make available the whole range of deuterated prostaglandins and their metabolites. Finally, the bioassay field is desperate for specific and if possible competitive antagonists to permit identification of individual members of the arachidonic acid-prostaglandin cascade.

There are also special problems in each of the three procedures. In particular, there is need to determine the nature of the so-called PGA fraction detected in the human blood RIA, whose level is modified by indomethacin.

The actions of the prostaglandins (and intermediate compounds and other biosynthetic products of the precursor, arachidonic acid) on airways depend on several factors including: the type of compound, the method of its application or administration, the dose and the existing tone of airway smooth muscle. Endoperoxides are 8-10 times as active as $PGF_{2\alpha}$ (*in vitro*), and thromboxane A_2 is >100 times as active as the endoperoxides, all being bronchoconstrictors. PGE_1 and E_2 relax trachebronchial smooth muscle *in vitro* and in anesthetized animals, but fail to induce bronchodilation in human subjects either intravenously or by aerosol (in the latter case, possibly because of upper airway irritation resulting from their low pH). PGE_2, in large doses, may constrict isolated guinea pig trachea and, conversely, $PGF_{2\alpha}$ may relax the same tissue preparation if it has been previously contracted by neostigmine. The actions of prostaglandins on airways may have physiologic significance, as in promoting bronchodilation during hyperventilation (PGE),

and shifting ventilation to better oxygenated regions of the lung ($PGF_{2\alpha}$, in localized edema). Prostaglandin release in the lung (from lung tissue or platelets) is likely to have a pathogenetic role in disease states, as in anaphylaxis, pulmonary embolism or edema. The possible use of prostaglandins or derivatives as bronchodilators in humans remains an unfulfilled promise.

Arachidonic acid increases pulmonary vascular resistance in the dog, though its potency is 1:10 times that of PGE_2 and 1:300 times that of $PGF_{2\alpha}$. Indomethacin blocks this response to arachidonic acid (AA). When the lung is perfused with dextran instead of blood, the response to AA is enhanced, perhaps because of some binding of AA to plasma proteins. Platelets, therefore, contribute little or nothing to the pulmonary vascular response to AA. The primary prostaglandins (PGE_2 and $PGF_{2\alpha}$) increase pulmonary vascular resistance in dogs, swine, and lambs (PGE_2 weakly and $PGF_{2\alpha}$ strongly). However, endoperoxides are the most active, being approximately 10 times as active as $PGF_{2\alpha}$. This suggests that these intermediate compounds may be active forms of the prostaglandin system in the lung. These intermediates also produce powerful contractions of isolated smooth muscles from intrapulmonary vessels and airways.

The airways, <u>in vivo</u>, are subject to many modulating substances, e.g., steroids, catecholamines, autonomic innervation, and vaso-active mediators. These inputs summate intracellularly to set the point at which airway smooth muscle rests. The role of prostaglandins in this process may be deduced by examining: (1) whether isolated airways respond to prostaglandins, (2) whether isolated airways synthesize prostaglandins, and (3) whether

inhibition of prostaglandin synthethase in vivo affects airway sensitivity or mechanics. In uncontracted preparations, small concentrations of PGE_1 and PGE_2 contract isolated guinea pig spirals. As concentration increases, the response reverses to relaxation. Indomethacin potentiates E_1 and E_2 contractile responses, but has no effect on relaxation. $PGF_{2\alpha}$ contracts the guinea pig trachea but the preparation is relatively insensitive. In over 60% of the preparations, the responses are tachyphylatic. Changes in Ca^{++} do not affect the tachyphylaxis, but nonsteroid anti-inflammatory drugs abolish tachyphylaxic and, as with $PGF_{2\alpha}$, inhibition of prostaglandin synthesis potentiates responses to the agonist. The mechanism of this potentiation is unclear but may be related to inhibition of a release of PGE_2 which would modulate the contractile effects of the agonists. This work needs to be confirmed. Slight biological activity has been measured for 13-14 dihydro $PGF_{2\alpha}$, but 15-keto $PGF_{2\alpha}$ is biologically inert. PGE_1 and PGE_2 relax airway preparations contracted with histamine. The metabolites, 15-keto PGE_1 or E_2, 13, 14-dihydro PGE_1 are about five times more active than PGE_2 and the metabolites are 50 to 100 times less potent than the parent prostaglandins.

Preparations contracted with histamine, barium, potassium, acetylcholine, serotonin, or nerve stimulation release PGE_2 which modulates contraction in vitro. The release is blocked by specific receptor blockade, e.g., antihistamine, if histamine is the agonist. This synthesis is not calcium dependent, but is apparently related to membrane distortion induced during the development of active tension in muscle. Treatment of guinea pigs with indomethacin or flufenamate does not affect total lung volume, respiratory frequency, dynamic lung compliance, or

airways resistance. Nor is airway sensitivity to the broncho-constrictor effects of histamine affected. Chronic isoproterenol or ascorbic acid treatment reduce airway sensitivity to histamine. These effects have been completely reversed with nonsteroid anti-inflammatory drugs, but have been unaffected by β-blockade once the effect was induced. However, the induction of this protective effect can be prevented by first administering β-blockers (e.g., propranolol). The data suggest that chronic isoproterenol or ascorbic acid treatment stimulates the synthesis of PGE_2 in airways which then modulates contraction. Agents that induce PGE_2 production in airways may be useful therapeutic tools in treating asthma or other disease states characterized by airway hypersensitivity.

Role of Prostaglandins in Lung Disease and Therapy

Prostaglandin $F_{2\alpha}$ is a potent bronchoconstrictor in a variety of lung preparations *in vitro* and *in vivo*. Asthmatics are exquisitely sensitive to $PGF_{2\alpha}$, showing a greater sensitivity to this agent, relative to normal subjects, than to other bronchoconstrictor drugs. These are some possible explanations:

1. Release of other mediators by $PGF_{2\alpha}$;
2. Sensitization by $F_{2\alpha}$ to the contractile action of other mediators;
3. Altered sympathetic - parasympathetic balance;
4. Smooth muscle sensitization to $F_{2\alpha}$ (receptor change, cell membrane change);
5. Increase in cyclic GMP;
6. Altered catabolism of $PGF_{2\alpha}$.

In spontaneous release of prostaglandins from human and guinea pig lung fragments, the parenchyma releases more PGF than PGE, and the trachea releases more PGE. In addition to anaphalaxis, antigen sensitization appears to increase the release of prostaglandins. Other mediators, e.g., histamine and slow-reacting substance, also release prostaglandins.

In the guinea pig, antigen-antibody induced bronchoconstriction is due to the release of histamine and prostaglandins, and can be blocked by a combination of an antihistaminic and an aspirin-like drug. However, bradykinin release of prostaglandins is different in different animal species. In the human lung, more PGE than PGF is released by antigen-antibody interaction. In

control tissue without antigen, the reverse is true. Indomethacin does not affect histamine release, but completely blocks PGE release. Human lung tissue shows little ability to metabolize PGE and PGF in the presence or absence of antigen.

The following questions about prostaglandins have not been answered, but probably could be answered with present technology:

1. Which of the prostaglandins are synthesized by human lung tissue?
2. Which of the prostaglandins are synthesized by human lung tissue during antigen-antibody induced release of mediators?
3. How effective are antihistaminics in controlling the symptoms of rhinitis or bronchial asthma?
4. How effective is aspirin in controlling the symptoms of rhinitis or bronchial asthma?
5. How effective is the combination of antihistaminics and aspirin in controlling the symptoms of rhinitis or bronchial asthma?
6. How effective is the combination of antihistaminics and an anti-SRS-A agent in controlling the symptoms of rhinitis or bronchinal asthma?

Histamine can cause a mediator response and influence other responses. Prostaglandins are generated in inflammatory conditions. Exogenous prostaglandins can stimulate mediators. Release of histamine is a secretory process. Human basophils secrete histamine. Histamine release is inhibited by increased intracellular cyclic AMP levels.

The latter may be caused by β-adrenergic agonists, histamine feedback through histamine β-receptors, or prostaglandins ($E>A>B>F_{2\alpha}\cong 0$). Changes in cyclic AMP parallel a decrease in histamine release. Histamine release is divided into two stages: (1) antigen actuation in the absence of Ca^{++} and (2) histamine release upon addition of Ca^{++}. Prostaglandins and all agents that control cyclic AMP work only in the first stage. The control of release of other mediators from basophils and mast cells is similar. The control of lysosomal enzyme release from polymorphonuclear leukocytes is also similar. In the first stage, arachidonic acid inhibits and indomethacin potentiates release. Are they acting intracellularly or extracellularly? What is the relevance in vivo? Histamine feeds back to inhibit histamine release. Do prostaglandins behave similarly? If so, do they operate through classic pharmacologic receptors on membranes or intracellularly? Prostaglandins might not be primary mediators, but might control the release response to other mediators.

Thinking about immediate type hypersensitivity reactions must focus not only on the pathopharmacologic response, but also on the inflammatory phase. The former is characterized by edema and alteration in muscle tone, should be highly reversible, and is most unlikely to account for the chronic disease, since cellular infiltration is in fact the hallmark of such circumstances; the irritability of the asthmatic airway could either result directly from cellular infiltration, or from biochemical changes elicited by the entire pharmacologic and inflammatory reaction sequence.

The mast cell, interestingly enough, is capable of elaborating a diverse collection of mediators, which can account for edema, change in muscle tone, infiltration with specific cell types, and activation of diverse secondary cell types. One of the infiltrating cell types, the eosinophil, has the capacity to inactivate the mediators of the pharmacologic phase of the reaction. In other words, as the response moves in to the inflammatory phase, the pharmacologic phase is terminated, presumably because its real role was to shift the reaction to the inflammatory phase, bringing in the essential ingredients of host defense. The fact that this response is detrimental, rather than beneficial, is of course characteristic of all immunologically mediated disease, and relates either to excessive immunologic activation, or some biochemical defect in control. It is thus essential to define the chemical structure and action of each of the chemical mediators of immunologic reactions. At the same time, it is critical to begin to identify the control mechanisms of their action. Such control mechanisms could reside in the lung itself, as well as in infiltrating cell types.

The role of prostaglandins in hemorrhagic and endotoxin shock has been studied in dogs by bioassay of carotid arterial and renal venous blood. In the initial phase of hemorrhagic shock, a substance appeared in the arterial blood which had biological properties and its appearance was not prevented by indomethacin pretreatment.

Hemorrhage was associated with renal vasoconstriction and high levels of angiotensin and catecholamines. In the late phase (decompensation) there was evidence of renal prostaglandin release; however, the prostaglandin was inadequate to overcome the renal constriction. Angiotensin antagonists cause a dramatic renal vasodilation. In the initial phase of endotoxemia, there was a prostaglandin-like (but not authentic prostaglandin) substance in the arterial blood. In the second phase (about 60 minutes) renal venous effluent (but not arterial) contained a PGE-like material associated with renal vasodilation and decreasing blood pressure. This material extracted like authentic PGE_2 and its release was blocked by indomethacin (which caused blood pressure elevation). Indomethacin caused marked renal vasoconstriction.

The mortality of patients in septic shock has been 50-70% for the past 20 years. Prostaglandins are among the implicated mediators. What are the levels of prostaglandin in an LD_{50} dog model? Are there changes in relation to the hemodynamic course? Can prostaglandin synthetase-inhibitors in clinical doses modify prostaglandin production or alter the effect? In baboons, prostaglandins are released, correlated with the acute hemodynamic events, can be modified by aspirin and indomethacin, but survival is significantly improved with aspirin and indomethacin. With an LD_{50} endotoxin dose, dogs are kept alive with indomethecin pretreatment. Aspirin and indomethacin should be used in clinical trials in high-risk patients with septic shock.

Alveolar hypoxia causes pulmonary vasoconstriction. Hypoxia may exert this effect either by a direct action on the vascular smooth muscle or by causing the release of chemical mediator(s) such as a prostaglandin. While in the cat, pretreatment with aspirin attenuates the hypoxic pressor reaction, in the dog, calf, and rat, when the synthesis of prostaglandins was inhibited by indomethacin or meclofenomate, the pulmonary pressor response to hypoxia was enhanced, not blocked. Therefore, it may be that in these species hypoxia stimulates the synthesis of a dilator prostaglandin which modulates but does not mediate the vasoconstrictor response. Minute doses of endotoxin prevent hypoxic pulmonary vasoconstriction, but this action of endotoxin is blocked by indomethacin. Therefore, it may be that endotoxin stimulates the production of a dilator prostaglandin which opposes the constrictor effect of hypoxia. The vasoconstrictor effect of vasoactive agents $PGF_{2\alpha}$, 2-methyl-histamine, and serotonin, is significantly influenced by alveolar O_2 tension.

During pulmonary edema, in isolated cat lungs, intact cats, or dogs, induced by raising pulmonary capillary pressure, vasoactive substances are present in edema fluid and foam and, to a lesser extent, in pulmonary perfusate. These substances include biologically active lipids ($PGF_{2\alpha}$, its 15 keto, 13, 14-dihydro derivative, and others), and two newly identified vasoactive lung peptides. One of the latter is biologically and immunologically related to the vasoactive intestinal polypeptide, and can therefore be assayed by the same radioimmunoassay; the other has opposite actions on smooth muscle organs (i.e., is spasmogenic) and its presence may be inferred only from bioassay of peptide extracts of foam or perfusate. The possible role of these compounds in the pathogenesis of pulmonary edema remains to be determined.

Recommendations

The following research needs and specific requests were expressed:

1. Increased availability of authentic standards, beginning with arachidonic acid and including all known active compounds and their metabolites.

2. Specific antibodies against metabolites of active compounds.

3. Better understanding of control of metabolic and biosynthetic pathways; generation of arachidonic acid; limiting steps; means, if any, of stimulating PGE versus PGF synthesis.

4. Development of specific antagonists or blockers at various steps of synthetic reactions.

5. Standardization of assays.

6. Histochemical localization of synthesis and metabolism.

7. Separation of cell types to permit study of their separate contributions to synthesis and metabolism.

8. Degradative enzymes: role and regulation.

9. Effects of chronic inhibition of PG biosynthesis (e.g., by indomethacin).

10. Other effects of anti-inflammatory agents?

11. Stimulation of human research.

12. Mechanisms of transport of prostaglandins? Active transport?

13. Interrelationships with other vasoactive mediators.

14. More workshops like this one!

AGENDA
PROSTAGLANDINS AND THE LUNG

January 21 and 22, 1976
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Co-chairmen: Sami Said and Peter Ramwell

Opening Remarks	Claude Lenfant Sami Said

Biochemistry and Biology of Prostaglandins and Related Substances

Moderator: Peter Ramwell

Prostaglandin and Arachidonic Acid Systems

Metabolic Pathways	Elizabeth Granstrom
Pharmacology of Arachidonic Acid	Peter Kot
Platelet Role in Prostaglandin Systems	Peter Ramwell

Metabolism of Prostaglandins

Fate of Prostaglandins in Human Lungs in Situ	C. Norman Gillis
Localization and Dynamics of Prostaglandin Metabolism	Una Smith Ryan
Prostaglandin Release in the Lung by Endogenous Substances	James Aiken

Biological Effects of Prostaglandins

Effects on Airways	Sami Said
Influence of Prostaglandins on the Pulmonary Circulation	Philip J. Kadowitz
Prostaglandin and Airway Responses in the Guinea Pig, *In Vitro* and *In Vivo*	James Douglas

Measurement and Assay of Prostaglandins

Analysis of Prostaglandins and Prostaglandin Metabolites by Gas Chronatography - Mass Spectrometry	Jurgen Frolich Richard Wharton
Radioimmunoassay	Lawrence Levine
Bioassay	Norberto Terragno

Role of Prostaglandins in Lung Disease and Therapy

Moderator: Sami Said

Airways Disease

Sensitivity to and Release of Prostaglandin F2	Aleksander A. Mathe
Immunorelease of Prostaglandins	Marion Webster
Prostaglandins and Mediator Release from Leukocytes	Larry Lichtenstein
Perspectives on Mediators in Airways Disease	K. Frank Austen

Pulmonary Vascular Diseases

Hemorrhagic and Endotoxic Shock	Philip Needleman
The Arachidonic Acid - Prostaglandin System in Endotoxic Shock	J.R. Fletcher
Endogenous Prostaglandins in Hypoxic Pulmonary Hypertension	Robert Grover
Pulmonary Edema	Sami Said

Approaches to Manipulation of Prostaglandin Phenomena

Open Discussion, Catalyst	Peter Ramwell
Summary and Comments	Peter Ramwell Sami Said

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